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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,374	06/08/2001	Jeffrey C. Rapp	AVI-007N	2448

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EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/877,374	RAPP, JEFFREY C.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9-29,62-70 and 72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-29,62-70 and 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 12/4/06, has been entered. Claims 10, 13, 19, 21, 23, 25, 26, 28, 64, 68-70 are amended; claims 1-5, 9-29, 62-70, and 72 are pending and under current examination.

Claim Objections

The prior objection of claim 71 is withdrawn in view of Applicants' cancellation of the claim.

The prior objection of claim 10 is withdrawn in view of Applicants' amendment to the claims.

Claim Rejections - 35 USC § 112

The rejection of claims 1-5, 7, 9-29, 62-72 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn. In particular, Applicants' arguments are found to be persuasive with regard to making of heterologous antibodies using oviduct cells in culture, as well as Applicants' arguments with regard to the amount of yield of antibodies produced from said methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 9-17, 19-29, 62 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* (WO 00/75300 A2, published June 2, 2000,

cited previously) when taken with Sanders *et al.* (**Biochemistry**, 27: 6550-6557, 1988), in further view of Mohammed *et al* (Immunotechnology, 4: 115-125, 1998 cited previously) and in further view of Michael *et al.* (U.S. Pat. No. 6,143,599, published November 7, 2000, cited previously)). This is a new ground of rejection.

The claims are directed to methods of producing heterologous antibodies in an avian oviduct cell, comprising, culturing the avian oviduct cell transfected with at least one expression vector comprising a nucleotide sequence encoding an immunoglobulin polypeptide under conditions which allow for the expression of the nucleotide sequence, and culturing the avian cell under conditions wherein the avian cell produces an immunoglobulin polypeptide that selectively binds an antigen or an immunoglobulin polypeptide that, when isolated and then combined with a light or heavy chain, forms an antibody that selectively binds the antigen; isolating the immunoglobulin produced by the cultured cells; thereby producing a heterologous antibody. Further embodiments limit the immunoglobulin polypeptide, the species of avian cell; the type of expression vector.

Ditullio teach methods of generating transgenic avian. Ditullio teach that the avian cell can be targeted either *in vitro* or *in vivo* [see pp. 7-10]. The avian species can be, for example, a chicken [see p. 2, lines 9-12]. DiTullio teach that the nucleic acid can contain a sequence encoding an antibody or fragment thereof, for example, a monoclonal antibody, or a chimeric molecule [*e.g.,* containing antibody portions of both murine and human origin] [see p. 2, lines 22-28]. Ditullio discuss the transcriptional regulatory elements that are contained in the nucleic acid construct, such as initiation signals, enhancers, promoters, which induce or control the transcription of protein coding sequences to which they are operably linked [see p. 3, lines 1-5]. For example, the promoter may be constitutive or inducible, and may be tissue-specific, inducible by external signals or within an intron [see p. 3, lines 12-15]. Ditullio teach that the chicken lysozyme or ovalbumin promoter may be used with the described transgene construct [see p. 3, lines 15-17]. In particular,

they teach transgene expression cassette in which the heavy and light chain coding regions of an antibody are ligated together, each under the direction of its own promoter operably linked to a matrix attachment region [see p. 3, lines 24-26]. Accordingly, Ditullio teach expression of an avian cell *in vitro* with a vector that comprises a nucleotide sequence encoding an immunoglobulin polypeptide.

Ditullio *et al.* differ from the claimed invention in that they do not specifically teach producing the antibody in an avian oviduct cell. However, prior to the time of the claimed invention, Sanders teach utilizing chicken oviduct cell systems *in vitro* to express heterologous genes. In particular, they teach that the regulatory elements of chicken oviduct cells, with regard to steroid receptors, have been well characterized, and thus, the cells can be regulated by, for example, estrogen, to express heterologous genes of interest. See page 6550, 1st col, and 2nd col., last ¶. In particular, Sanders teach using tubular gland cells, which are primary oviduct cells, isolated from chickens (see p. 6551, 1st col., 1st ¶), which were then transfected with various plasmids.

Although Ditullio teach that the cell can be targeted *in vitro* or *in vivo*, they do not contemplate that the cell can produce an antibody outside of the context of producing a transgenic avian that produces the antibody. However, prior to the time the claimed invention was made, Mohammed teach expression of recombinant human antibodies in stably transfected DT40 cell lines. In particular, Mohammed teach that two types of vectors were developed, one with the heavy chain of the immunoglobulin which results in the expression of a murine anti-dansyl variable region joined to the appropriate human heavy chain constant region. The other vector encodes the light chain which results in the expression of a corresponding murine anti-dansyl variable region joined to a human kappa light chain constant region. [See pp. 116-117, bridging ¶]. Mohammed teach that these two vectors were co-transfected with each of the vectors into a chicken B lymphoblastoid cell line, DT40 [see p. 117, section 2.2.]. The transfected cells were maintained in

culture media for two days, wherein surviving colonies were screened by ELISA to verify expression of the chimeric antibodies.

Ditullio, Sanders and Mohammed differ from the claimed invention in that they do not teach or suggest the expression vector further encodes a second immunoglobulin polypeptide and an IRES (claim 3), that the vector is a viral vector (claims 9-10), and that the promoter is the cytomegaloviral promoter (claim 13), and they do not teach isolation of the immunoglobulin from the cultured cells. However, prior to the claimed invention, Michael teach producing cells that express monoclonal antibodies, wherein the cells are screened for the antibody of interest, by, for example, measuring the binding of the antibodies (co. 2-3, bridging ¶), and specifically teach *in vitro* transfection of cells, culturing of the cells, and then isolating the antibody from the cells (col. 3, lines 15-27). Furthermore, Michael teach methods of producing monoclonal antibodies in an avian system, and in particular, chickens. They teach that the CMV immediate early gene promoter is a promoter that can be used to obtain high-level of expression of a coding sequence of interest, and that by employing such a well-known promoter, the level and pattern of expression can be optimized (see col. 16, lines 47-63). Michael further teach that the use of IRES elements can create multigene, or polycistronic messages. They teach that IRES elements can be linked to heterologous open reading frames, and that by virtue of the IRES element, multiple genes can be efficiently expressed by a single promoter or enhancer to transcribe a single message [col. 19, lines 5-21]. Michael teach that genetic constructs can be introduced into cells by both viral and non-viral transduction. Viral methods include adenoviral, and adeno-associated viral vectors [col. 19, lines 30-45].

Accordingly, in view of the combined teachings of Ditullio, Sanders, Mohammed and Michael, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the methods of generating antibodies from avian cells, as taught by Ditullio, in cells such as

tubular gland cells (which are avian oviduct cells), as taught by Sanders, by use of the cytomegaloviral promoter, an IRES element, or by use of a viral vector, as well as isolating immunolgloublins produced by the cultured cells, as taught by Mohammed and Michael, with a reasonable expectation of success.

One of ordinary skill would have been sufficiently motivated to make such a modification, because the isolation of antibodies directly from cultured cells, such as oviduct cells, would be more efficient than producing a transgenic bird, and further, the cytomegaloviral promoter is a well-known and well-characterized promoter that would allow for optimal levels and patterns of gene expression, that utilizing an IRES element would facilitate expression of multiple genes, and that viral transduction is an efficient way to deliver a construct to a cell. Finally, it is noted that the claims do not require a yield of antibody produced by the oviduct cells, therefore, it is well known in the art that one of skill could readily isolate these antibodies (as supported by Mohammed and Michael).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken Sanders, in further view of Mohammed, and in further view of Michael *et al.* as applied to claim1-5, 9-17, 19-29, 62 and 63 above, and further in view of Larocca *et al.*, US. Pat. No. 6,448,083 (Issued September 10, 2002, filed February 26, 1999).

Ditullio *et al.*, Sanders and Michael *et al.* are described above. They provide the requisite teachings and motivation to produce antibodies from an avian oviduct cell, by culturing a transfected avian oviduct cell and isolating antibodies therefrom. However, they do not specifically teach that the expression vector comprises a region encoding a bovine growth hormone transcriptional terminator.

However, prior to the time the claimed invention was filed, Larocca teach vectors that can be used in order to express a transgene in mammalian cells. In particular, these vectors can be used for expression in mammalian cells, and can include various components, including termination sequences (see col. 19, lines 56-61), and in particular, utilizing a vector containing a bovine growth hormone tracnsriptional terminator. See col. 34, lines 33-36.

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to use the vector, as taught by Larocca, with the methods of culturing avian oviduct cells to produce antibodies, as taught by Ditullio *et al.*, Sanders and Michael *et al.,* with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification, because the vector taught by Larocca would allow for monitoring and expression of the transgene (see Example 1).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 64-69, 70 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken Sanders, in further view of Mohammed, and in further view of Michael *et al.* as applied to claims 1-5, 9-17, 19-29, 62 and 63 above, and further in view of Ling *et al.* (Genomics, 60:341-355, 1999, cited previously) and Najarfian *et al.* (Exp. Opin. Invest. Drugs, 9(9): 2147-2167, 2000, cited previously).

Ditullio *et al.*, Sanders and Michael *et al.* are described above. They provide the requisite teachings and motivation to produce antibodies from an avian oviduct cell, by culturing a transfected avian oviduct cell and isolating antibodies therefrom.

However, they do not specifically teach producing an antibody specific for CTLA4. However, prior to the time the claimed invention was made, Ling teach the sequence of human CTLA4, including its alignment with the mouse CTLA4

sequence. See Figure 3. Ling teach that CTLA4 has been correlated with specific diseases (see p. 341, 2nd column). Najarfian provide the requisite motivation for the production of CTLA4 antibodies, as instantly contemplated. They teach that CTLA-4 is only expressed on activated T-cells, and that CTLA-4 negative signaling pathways may be required for the induction of acquired tolerance. See p. 2148, 2nd column, Introduction.

Accordingly, in view of the combined teachings, it would have been obvious for the skilled artisan to modify the technique of producing antibodies in avian oviduct cells, as taught by the combined teachings of Ditullio, Sanders, Mohammed and Michael, utilizing a construct encoding CTLA-4, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification, as the art recognizes the importance of suppressing CTLA-4 to generate acquired tolerance, for example.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

thaian ton

THAIAN N. TON
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